Impact of left ventricular volume/mass ratio on diastolic function

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Aims
To assess the impact of left ventricular (LV) volume/mass ratio on diastolic function parameters in subjects with dilated cardiomyopathy (DCM) or hypertrophic cardiomyopathy (HCM) and healthy controls.

Methods and results
We performed echocardiography in 44 healthy controls, 35 HCM subjects, 29 DCM subjects with narrow QRS complex (DCM-n), and 27 DCM subjects with wide QRS complex (DCM-w). Mitral annulus velocity (Ea) and trans-mitral E-wave velocity were used to estimate time constant of isovolumic pressure decay (τ). LV flow propagation velocity (Vp) and early intraventricular pressure gradient (IVPG) were derived from colour M-mode of LV inflow. We calculated LV twist and peak untwisting rate (UntwR) by speckle tracking. Mean LV volume/mass ratio was 0.34 ± 0.09 mL/g in healthy controls, 0.15 ± 0.06 mL/g in HCM, 0.6 ± 0.2 mL/g in DCM-n, and 0.8 ± 0.3 mL/g in DCM-w patients (P < 0.001 for all groups). Resting LV ejection fractions were 63 ± 7, 64 ± 8, 31 ± 8, and 26 ± 8%, respectively (P < 0.01 vs. controls for DCM groups). In a multivariate analysis, LV volume/mass ratio remained a strong independent predictor of Vp (P = 0.001), IVPG (P = 0.009), and UntwR (P < 0.001) but not for Ea (P = 0.25).

Conclusion
LV volume/mass ratio had influences on diastolic function parameters independent of intrinsic diastolic function and filling pressures. It should be considered when assessing patients suspected of LV diastolic dysfunction.

Keywords
Left ventricular volume/mass ratio • Diastolic function • Dilated cardiomyopathy • Hypertrophic cardiomyopathy • Ventricular torsion (twist) • Echocardiography

Introduction
A wealth of data supports patient classification into specific diastolic dysfunction groups based on various parameters of left ventricular (LV) filling.1–5 This classification correlates with objective measures of cardiovascular performance such as pulmonary capillary wedge pressure (PCWP) or the time constant of isovolumic pressure decay6–10 and is also a predictor of patient’s symptoms and survival. The classification bases on the transmural and pulmonary vein flow profiles and on isovolumic relaxation time (IVRT). However, the past decade introduced new markers of diastolic function that are based either on intraventricular flow or LV wall motion.11 The need for these newer parameters was driven by the U-shaped relationship between the ratio of early-to-late trans-mitral flow velocity (E/A) with filling pressure and facilitated by technical developments in echocardiography.

Engineering insight, as well as a modelling study,12 suggests that some new markers of diastolic function, such as colour M-mode flow propagation velocity (Vp), are affected by LV dilation or presence of concentric hypertrophy. This implies that values of Vp considered normal in the setting of dilated cardiomyopathy (DCM) may be abnormal in hypertrophic cardiomyopathy (HCM). For these reasons, we conducted a study to assess the way diastolic function parameters behave in the presence of
altered LV volume and mass (both represented by LV volume/mass ratio) as seen in DCM or HCM. A primary aim of this study was to determine whether LV volume/mass ratio affects parameters of diastolic function.

### Methods

#### Study population

**Patients**

To identify patients, we first cross-referenced a list of patients for which the echocardiography report stated the presence of hypertrophic (n = 810) or non-ischaemic DCM (n = 940) with a database of 12,768 Cleveland Clinic patients in whom echocardiography was performed on a Vivid 7 ultrasound machine (GE Medical, Milwaukee, WI, USA) in a period of January 2004–December 2007. The medical records were then checked to ascertain that inclusion criteria were satisfied as follows:

- HCM was diagnosed by the echocardiographic demonstration of a hypertrophied, non-dilated LV in the absence of other acquired or congenital heart disease. Non-ischaemic DCM was diagnosed in a presence of dilated left ventricle with ejection fraction <40%, no prior history of myocardial infarction, and no significant coronary artery stenosis on coronary angiography. DCM subjects were subcategorized according to QRS width into DCM with narrow QRS (<130 ms, DCM-n) or DCM with wide QRS (≥130 ms, DCM-w).
- Finally, patients were selected if acquired echocardiography study was of a satisfactory quality (35 from 55 HCM subjects, 29 from 40 DCM-n subjects, and 27 from 46 DCM-w subjects) as indicated in Data acquisition section.

All patients were clinically stable and in normal sinus rhythm. Patients were excluded for significant valvular heart disease (mitral regurgitation was allowed if it was less than moderate degree), pacemaker implantation, prior cardiac surgery, or percutaneous LV septal reduction procedure. According to aforementioned criterions, all patients were identified (n = 94, age 53 ± 14 years, range 22–79 years).

**Control subjects**

Our healthy controls were selected from our database of 102 normal subjects. These subjects volunteered for an echocardiography study after being informed through information panels located throughout Cleveland Clinic main campus. Subjects were declared healthy after normal electrocardiogram and thorough medical history and physical examination (including testing of fasting blood glucose and cholesterol fraction levels) revealed no cardiovascular disease. None of them reported taking cardiac medications (except aspirin). To assess the impact of aging on diastolic function, we first randomly sampled healthy controls out of this population (n = 74; average age 41 ± 15 years, range 18–76 years). This sample size yields a two-sided power (beta) of 80% to detect a correlation of 0.325 or greater at the alpha level of 0.05. To assess the differences in diastolic function between healthy controls and subjects with cardiomyopathy, we age-matched these two groups. For this purpose, we sub-sampled our 74 healthy controls by, first, limiting the selection by having the age range identical to the age range of patient sample, and then drawing all possible samples with the size of n > 40 subjects. The selected sample had a closest mean and SD to the patients’ sample (n = 44, age 50 ± 13 years, range 22–76 years, P=n.s. for the comparison between patients and controls).

Institutional Review Board of Cleveland approved for the database search. All subjects gave written informed consent for the participation in respective prospective studies.

#### Data acquisition

Transthoracic two-dimensional echocardiography was performed with a Vivid 7 ultrasound machine (GE Medical Systems, Milwaukee, WI, USA) and M3S/M4S probe. Standard views, including apical four-chamber, apical two-chamber, apical long-axis, and parasternal long- and short-axis views, were obtained. Short-axis views were acquired at the mitral valve and apical LV levels (absence of right ventricle and papillary muscle for apical short-axis). Second-harmonic images were acquired with high frame rate B-mode scans (40–90 frames/s) for speckle tracking imaging. Pulsed-wave Doppler interrogation of the transmural flow and LV outflow tract (LVOT), and colour M-mode of intraventricular filling were acquired from apical four-chamber view. Two-dimensional tissue Doppler image followed by pulsed-wave assessment of the septal and lateral mitral annulus (Ea) were also obtained in the apical four-chamber view. All images were stored in a digital cine-loop format for off-line analysis.

#### Data analysis

LV end-diastolic and end-systolic volumes, ejection fraction, and left atrial end-systolic volume were calculated by a modified Simpson’s biplane method from apical imaging planes. LV mass was calculated by the area—length formula recommended by the American Society of Echocardiography. LV transverse diameter in end-systole was calculated from the LV short-axis area at papillary muscle level using equation LV diameter = 2 × 2 × (LV area/3.14)0.5. All cardiac chamber volumes and mass measures were indexed to body surface area. We assumed that LV volume at the beginning of filling (i.e. at the end of isovolumic relaxation) could be represented by end-systolic volume. Thus end-systolic volume/mass ratio was taken to represent a feature of LV geometry at the beginning of LV filling.

Peak velocity of early (E) and late (A) wave of transmural flow and E-wave deceleration time (DT) were measured from the pulsed-wave Doppler obtained at the tip of mitral leaflets. Aortic valve closure and mitral valve opening times were obtained from pulsed-wave Doppler signal properly positioned at LVOT to calculate LV IVRT. We derived two parameters of intraventricular filling, flow propagation velocity (Vp), and the peak early diastolic intraventricular pressure gradient (IVPG), from colour M-mode at LV inflow. Ea was the average of septal and lateral annulus velocities. All values were averaged from three cardiac cycles.

Rotational rates of the LV base and apex were measured from short-axis echocardiographic images by speckle tracking (EchoPac PC software, GE Medical) as described previously. In brief, the instantaneous difference of basal and apical rotational rates was calculated, yielding the twisting rate (TwR) curve. Peak TwR and untwisting rate (UntwR) were then defined by peak positive and negative velocities, respectively. Twist was the peak value obtained by temporal integration of TwR curve. Two cardiac cycles of both basal and apical data were analysed and the data were averaged.

The time constant of isovolumic pressure decay with a zero asymptote assumption (τ0) was estimated using the following equation:

\[
\tau_0(\text{ms}) = \frac{IVRT}{\ln(P) - \ln(PCWP)}
\]

where P is systolic blood pressure and PCWP is mean PCWP. In HCM subjects with LVOT obstruction, peak LV systolic pressure was estimated by adding the peak LVOT gradient to sphygmonanometric systolic blood pressure. Mean PCWP was estimated by averaging PCWP obtained by two previously described estimation methods (i.e. EI/Vp and EI/Ea) to increase the accuracy of the estimation.
Impact of LV volume/mass ratio on diastolic function

Table 1  Clinical and echocardiographic findings of all subjects

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 44)</th>
<th>HCM (n = 35)</th>
<th>DCM-n (n = 29)</th>
<th>DCM-w (n = 27)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (year)</strong></td>
<td>50 ± 13</td>
<td>47 ± 14</td>
<td>54 ± 12</td>
<td>59 ± 12*</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Male (n)</strong></td>
<td>16</td>
<td>24</td>
<td>19</td>
<td>18</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>HR (b.p.m.)</strong></td>
<td>68 ± 11</td>
<td>58 ± 11</td>
<td>75 ± 16‡</td>
<td>72 ± 13‡</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>SBP (mmHg)</strong></td>
<td>120 ± 14</td>
<td>124 ± 18</td>
<td>115 ± 21</td>
<td>114 ± 18</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>DBP (mmHg)</strong></td>
<td>69 ± 9</td>
<td>73 ± 12</td>
<td>68 ± 14</td>
<td>70 ± 13</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>NYHA class</strong></td>
<td>1</td>
<td>2 ± 0.4</td>
<td>2.5 ± 0.6</td>
<td>2.5 ± 0.6</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>LVEDV (mL)</strong></td>
<td>32 ± 11</td>
<td>38 ± 17</td>
<td>127 ± 61‡</td>
<td>178 ± 98‡‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>LVEF (%)</strong></td>
<td>63 ± 7</td>
<td>64 ± 7</td>
<td>31 ± 8‡</td>
<td>26 ± 8‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>LVMI (gm/m²)</strong></td>
<td>60 ± 32</td>
<td>119 ± 39</td>
<td>112 ± 22</td>
<td>110 ± 28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>LV volume/mass ratio (mL/gm)</strong></td>
<td>0.32 ± 0.09*</td>
<td>0.16 ± 0.06*</td>
<td>0.60 ± 0.20*</td>
<td>0.80 ± 0.30*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>QRS width (ms)</strong></td>
<td>90 ± 18</td>
<td>108 ± 22</td>
<td>106 ± 12</td>
<td>156 ± 18‡‡</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

DCM-n-w, dilated cardiomyopathy with narrow(wide) QRS complex width; DBP, diastolic blood pressure; HCM, hypertrophic cardiomyopathy; NYHA, New York Heart Association functional classification; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-systolic volume; LVMI, left ventricular mass index; SBP, systolic blood pressure.

Last column represents overall significance level by the analysis of variance. Post hoc multiple group comparisons are shown as: *P < 0.001 vs. control; †P < 0.05 vs. control; ‡P < 0.001 vs. HCM; *P < 0.05 vs. HCM; †P < 0.05 vs. DCM-n.

Table 2  Important diastolic parameters in each group of subjects

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 44)</th>
<th>HCM (n = 35)</th>
<th>DCM-n (n = 29)</th>
<th>DCM-w (n = 27)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E-wave velocity (cm/s)</strong></td>
<td>71 ± 17</td>
<td>80 ± 21</td>
<td>76 ± 26</td>
<td>82 ± 32</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>E/A ratio</strong></td>
<td>1.3 ± 0.5</td>
<td>1.4 ± 0.6</td>
<td>1.8 ± 1.5</td>
<td>1.6 ± 1.2</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>DT (ms)</strong></td>
<td>204 ± 42</td>
<td>231 ± 70</td>
<td>173 ± 61‡</td>
<td>167 ± 68†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Vp (cm/s)</strong></td>
<td>62 ± 13</td>
<td>60 ± 16</td>
<td>37 ± 9†</td>
<td>35 ± 12‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>IVPG (mmHg)</strong></td>
<td>1.4 ± 0.5</td>
<td>1.5 ± 0.6</td>
<td>1.0 ± 0.4‡</td>
<td>1 ± 0.4‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Ea (cm/s)</strong></td>
<td>11.0 ± 2.4</td>
<td>7.1 ± 2.7‡</td>
<td>5.5 ± 1.9‡</td>
<td>5.3 ± 1.4‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Untwisting rate (°/is)</strong></td>
<td>113 ± 48</td>
<td>93 ± 55</td>
<td>48 ± 30‡</td>
<td>21 ± 15‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>tf (ms)</strong></td>
<td>35.6 ± 9.2</td>
<td>42.9 ± 12.0‡</td>
<td>56.3 ± 18.0‡</td>
<td>65.5 ± 19.1‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>LAVI (mL/m²)</strong></td>
<td>19.0 ± 6.8</td>
<td>29.8 ± 9.4*</td>
<td>37.4 ± 17.7*</td>
<td>37.5 ± 15.6*</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

E, early transmural inflow velocity; E/A ratio, ratio of early-to-late transmural flow velocity; DT, deceleration time; Vp, mitral flow propagation velocity; IVPG, early diastolic intraventricular pressure gradient; Ea, averaged mitral annulus velocity; tf, time constant of isovolumic pressure decay with a zero asymptote assumption; LAVI, left atrial volume index.

Other abbreviations and significance as in Table 1.

To assess the accuracy of tf estimation, we additionally analysed the data from a prospective study of echocardiography during acutely decompensated systolic heart failure, in which filling pressures were routinely monitored by a pulmonary artery catheter. From this study, we randomly selected 34 subjects (16 of whom with DCM) with 56 echocardiography studies performed within 30 min of PCWP measurement. We used these data to compare tf calculated using measured PCWP vs. tf estimated from echocardiography only data. We also identified nine of our patients with HCM had filling pressures measured invasively within 48 h of echocardiography, without any change of cardioactive medications in the meantime. The correlation of tf estimated by echocardiography with tf calculated from invasively recorded filling pressures had an of r = 0.70, P < 0.0001 (r = 0.71 for systolic heart failure subjects and r = 0.84 for HCM patients), while the average difference between two methods was 0.24 ms [95% confidence interval (CI) −2.76 to 3.24] with 95% limits of agreement (LOA) −23.56 ms (95% CI −18.7 to −28.46) to 24.04 ms (95% CI 18.9−29.1). Taken together, these data imply that our tf estimate is physiologically relevant even with PCWP estimation error.

Validation of LV mass estimation by echocardiography

We already validated estimation of LV mass by echocardiography using magnetic resonance imaging as a ‘gold standard’ in 16 healthy controls. We further assessed 10 HCM patients (eight with asymptomatic septal hypertrophy, one with concentric HCM, and one with proximal septal bulge, mean age 30 ± 9 years) and seven patients with DCM (all with E < 40%, mean age 57 ± 20 years), all of whom had a magnetic resonance imaging and echocardiography studies performed within 7 days. In a total group of 33 patients, a bias between two methods was 9.7% (95% CI −1 to 21%), with 95% LOA of −22% (95% CI −41 to −3%), and 42% (95% CI 23−61%). Specifically, it was 6.5%...
(95% LOA of –26 to 39%) in HCM subjects and 20% (95% LOA of –17 to 57%) in DCM subjects (see Supplementary material online, Figure S1).

Reproducibility
To assess intra- and inter-observer variability of LV volumes and mass, nine randomly chosen data sets (corresponding to 5% of our study population) were measured twice, after a time interval of 1 month, by the same observer and, at that time, also by a second observer blinded to the measurements of the first observer. Inter- and intra-observer variabilities were quantified as the difference and percent difference (with a denominator a mean of the two measurements) between the two measurements along with their 95% LOA.21 Intra-observer variability for LV end-diastolic volume, end-systolic volume, and mass was 0.9 mL (95% CI –9 to 7 mL) [95% LOA –19 mL (95% CI –35 to –5 mL) to 17 mL (95% CI 3–31 mL)], 0.5 mL (95% CI –3 to 4 mL) [95% LOA –21 (95% CI –45 to 3 mL) to 22 mL (95% CI –2 to 46 mL)], and 2.5 g (95% CI –19 to 24 g) [95% LOA –30 (95% CI –68 to 8 g) to 35 (95% CI –3 to 73 g)]. For the same three parameters, percent intra-observer variability was 0.2% (95% CI –2.7 to 2.3%) [LOA –4 (95% CI –8 to 0%) to 3% (95% CI 0–8%)], 0.5% (95% CI –3.2 to 4.2%) [95% LOA –5 (95% CI –11 to 1%) to 6% (95% CI 0–12%)], and –0.1% (95% CI –2.7 to 2.5%) [95% LOA –4 (95% CI –9 to 1%) to 4% (95% CI –1 to 8%)]. Inter-observer variability for LV end-diastolic volume, end-systolic volume, and mass was 7.8 mL (95% CI –19 to 35 mL) [95% LOA –33 (95% CI –80 to 14 mL) to 49 mL (95% CI 2 to 96 mL)], –2.3 mL (95% CI –9 to 5 mL) [95% LOA –13 (95% CI –25 to –1 mL) to 8 mL (95% CI –4 to 20 mL)], and –5 g (95% CI –22 to 12 g) [95% LOA –31 g (95% CI –61 to –1 g) to 21 g (95% CI –9 to 51 g)]. For the same three parameters, percent inter-observer variability was 1.3% (95% CI –1.9 to 4.5%) [LOA –4 (95% CI –9 to 2%) to 6% (95% CI 0–12%)], –0.7% (95% CI –3.0 to 1.6%) [95% LOA –4 (95% CI –8 to 0%) to 3% (95% CI –1 to 7%)], and –0.5% (95% CI –2.6 to 1.6%) [95% LOA –4 (95% CI –7 to 0%) to 3% (95% CI –1 to 6%)] (see Supplementary material online, Figure S2).

Statistical analysis
Values are shown as mean ± SD or percentage when appropriate. Between-group comparisons for individual parameters were done by analysis of variance followed by post hoc Tukey Honest Significant Difference test to correct for multiple comparisons. Correlation between diastolic parameters (Vp, IVPG, Ea, UntwR, and DT) and LV volume/mass ratio was performed by simple linear regression. We also assessed within-group correlations between diastolic parameters and LV geometry by analysis of covariance, with patient groups as an independent predictor and LV volume/mass ratio as a covariate.

Echocardiographic parameters of early diastolic function are affected by preload and relaxation. Since transmitral E-wave velocity is fully determined by preload and relaxation and τ0 is a direct measure of relaxation, we postulated that by correcting for transmitral E-wave velocity and τ0 we would eliminate effects of preload and relaxation on echocardiographic diastolic function parameters.22,23 Therefore, to
Further study the interaction between preload, relaxation, and LV volume/mass ratio on diastolic function we performed a multiple regression using transmitral E-wave velocity, $t_0$, and LV volume/mass ratio (with variance stabilized by taking a cubed root) as predictors. As dependent variables, we tested following five diastolic parameters of interest: $V_p$, IVPG, $E_a$, UntwR, and DT. Then, using regression analysis results, we corrected each diastolic parameter of interest for the values of transmitral E-wave velocity and $t_0$ by equation:

$$\text{corrected diastolic parameter}_i = \frac{\text{measured diastolic parameter}_i}{C_0(E_i/C_0\text{average})^{b_E} (t_i/C_0\text{average})^{b_t}}$$

Here, $E$ is E-wave velocity, $t$ is $t_0$, and $b_E$ and $b_t$ are corresponding regression coefficients, while subscript $i$ denotes values of individual patient. Linear regression of these corrected diastolic parameters with LV volume/mass ratio is identical to partial correlation data obtained from multiple linear regressions. A two-sided $P$-value of $<0.05$ was considered statistically significant for all tests, except for the results of linear regression analyses where $P < 0.01$ was considered significant to correct for multiple comparisons ($n = 5$) between LV volume/mass ratio and diastolic parameters.

### Results

Subjects’ clinical characteristics and basic echocardiographic findings were presented in Table 1. In HCM patients, the hypertrophy type was concentric in 15, asymmetric septal in 14, and septal bulge in six patients (four of which had also distal septal and/or posterior wall hypertrophy). Eleven HCM patients had resting LVOT gradient $\geq 30$ mmHg (range 33–115), with its magnitude correlating with LV mass ($r = 0.54$, $P = 0.0008$). Of note, LV volume mass ratio correlated strongly with LV end-systolic transverse diameter ($r = 0.85$, $P < 0.0001$), a more traditional parameter of LV size.

Diastolic echocardiographic parameters in each group of subjects are shown in Table 2. Although transmitral E-wave velocity and $E/A$ ratio were similar across the groups, all other diastolic parameters showed significant between–group differences. Examples of some important parameters from a representative case in each group of subjects were depicted in Figure 1.

### Effect of left ventricular volume/mass ratio on diastolic function

LV volume/mass ratio showed significant inverse relationship with unadjusted $V_p$, IVPG, $E_a$, and UntwR (Figure 2). As LV volume/mass ratio showed small variance within each patient group (Table 1), only UntwR showed significant within–group correlation with LV volume/mass ratio ($r = -0.28$, $P = 0.002$).

After adjusting for the impact of $E$ and $t_0$ by multiple regressions, LV volume/mass ratio remained a strong independent predictor of $V_p$, IVPG, UntwR, and DT ($P < 0.001$ for all) (Table 3 and Figure 3). In contrast, LV volume/mass ratio did not influence $E_a$. 

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**Figure 2** Correlation between LV volume/mass ratio and diastolic parameters derived from LV wall motion and intraventricular flow. Correlation between LV end-systolic volume/mass ratio (LV volume/mass ratio) and flow propagation velocity ($V_p$; panel A), early diastolic intraventricular pressure gradient (IVPG; panel B), averaged early diastolic mitral annulus velocity ($E_a$; panel C), and peak untwisting rate (UntwR; panel D), are shown.
As a resting LVOT gradient in HCM may indicate a presence of asymmetric hypertrophy, we repeated analysis after excluding 11 subjects with resting LVOT gradient of >30 mmHg. In this setting, LV volume/mass ratio was again a strong independent predictor of Vp (partial r = −0.47, P < 0.0001), IVPG (partial r = −0.34, P = 0.0001), UntwR (partial r = −0.44, P < 0.0001), and DT (partial r = −0.36, P = 0.0001). It also had a weak impact on Ea (partial r = −0.19, P = 0.03), probably reflecting a decreased sample size in the lower portion of distribution of LV volume/mass ratio values.

**Discussion**

Previous studies have shown that Vp, IVPG, Ea, and UntwR are strongly influenced by relaxation rate and displayed weak to moderate preload sensitivity. Here, we show that Vp, IVPG, UntwR, and DT were independently influenced by LV volume/mass ratio. In contrast, Ea was influenced by relaxation and preload only. In practical terms, these data indicate that depressed values of Vp, IVPG, and UntwR when observed in HCM reflect deeper abnormalities in relaxation than in DCM.

Computer modelling has shown that, in a normal ventricle, a doughnut-shaped vortex forms around the column of mitral inflow and then travels downward towards the apex. Increased LV size in DCM should increase vortex size because of a larger distance between blood column and LV walls. Large vortices dissipate energy that results in a loss of velocity of flow column. Baccani et al. used fluid dynamics model of DCM to prove that LV dilation indeed decreases Vp. Furthermore, they have shown that this is associated with the initial vortex staying attached to the mitral valve. Although they have not assessed IVPG, it can be surmised that it also decreases. By analogy, effects of LV volume/mass ratio in HCM should be opposite, because boundary effects of LV
do not allow energy dissipation. Here, we corroborate that parameters of intraventricular filling, $V_p$, and IVPG, are indeed decreased in DCM but frequently preserved in HCM (Table 2).

LV volume/mass ratio had influence on UntwR but not $E_a$, although they both represent early diastolic wall motion (Figure 3). The impact of LV volume/mass ratio on UntwR can be explained through its link with LV twist. LV twist is generated because subepicardial myocytes, oriented in a left-handed helix, have a lever advantage over subendocardial myocytes that run in a right-handed helix. As ventricles with HCM have a larger distance between endo- and epicardial layers, the subepicardial helix becomes even more dominant, twisting more forcefully the apex in the counterclockwise and the base in the clockwise direction. This increased twist allows for higher peak UntwRs. Thus, despite the fact that HCM is characterized by prolonged time to peak UntwR and worsened relaxation, which both decrease UntwR, this is offset by larger LV thickness, leading to higher UntwR in DCM assuming similar level of relaxation impairment. In contrast, it is puzzling that LV volume/mass ratio does not influence $E_a$ velocity. The presence of LV hypertrophy, independent of whether it is concentric (as in HCM) or eccentric (as in DCM), is sufficient to decrease $E_a$.

Another factor that can influence diastole is intraventricular conduction delay (IVCD) as represented by QRS width. IVCD may lead to dyssynchronous relaxation of LV regions by increasing dispersion of repolarization. However, in DCM, IVCD is predictive of disease severity, and thus it is difficult to dissociate effects of IVCD from that of severe DCM. Our study indicated that, while diastolic function parameters worsen with a degree of IVCD in a univariate analysis, after adjustment for LV volume/mass ratio, a loss of diastolic suction and ventricular recoil in DCM was independent of the presence of IVCD.

Clinical implications and future directions

Although new diastolic function parameters are being proposed continuously, only $E_a$ and $V_p$ have been tested for their prognostic value. Some studies showed that $E_a$ has incremental predictive power over and above clinical and standard echocardiography data, our group, albeit in a smaller study, failed to confirm the predictive value of either $E_a$ or $V_p$. On the other hand, prognostic value of $E_a$ and $V_p$ improves once they corrected for $E$-wave velocity. Our data imply that $V_p$, as well as IVPG, UntwR, and DT, have to be additionally corrected for underlying LV geometry. These findings are especially relevant, if clinical trials are planned to test these diastolic parameters.

An obstacle for a wider use of diastolic parameters, we assessed here is that they can be generated only by complex and time-consuming post-processing. Currently, only $E_a$ can be readily
derived from most ultrasound machines. However, this obstacle could be easily overcome, if the manufacturers of echo devices incorporate post-processing algorithms into standard ultrasound machines. Given a current level of development, this should be a simple engineering feat.

**Limitations**

We have not assessed LV volumes and mass using threedimensional methods such as magnetic resonance or threedimensional echocardiography, which may have introduced errors in the estimation of LV volume/mass ratio, especially in HCM patients. PCWP and $\tau_o$ were estimated by non-invasive means, which increased uncertainty in the estimation of the magnitude of the effect of relaxation on diastolic parameters. To overcome this, we studied a large patient population. The assessment of $\tau_o$ by our method has been tested in a variety of patient populations, but not specifically in HCM. However, basic mathematical principles should be universal to all patients. Ample evidences corroborate preload sensitivity of E-wave, especially when controlled for relaxation.\(^6,^{10}\) As our regression model always included relaxation, we believe that E-wave velocity well reflected the impact of preload. The most sensitive part of our $\tau_o$ estimation is the calculation of PCWP estimate. Although several studies indicated that E’ corrected by $E_o$ or $V_o$ is robust enough to detect changes in PCWP at a group level, this relationship seems poorer in thesetting of LV hypertrophy.\(^6\) However, our clinical data show the precision is satisfactory for making accurate $\tau_o$ estimation. It is uncertain whether our findings can be generalized to other patient populations, such as restrictive cardiomyopathy. Infiltrative processes that occur in amyloidosis or Fabry’s disease affect both wall thickness and structure, thus dramatically changing passive biomechanical characteristics of muscle tissue. Our aim was to assess whether a change of relative thickness of LV wall with preserved myocardial tissue characteristics affects diastolic function parameters. Additionally, HCM patients with LV outflow obstruction frequently display septal bulge or sigmoid shape of the septum that may have more impact on LV inflow than predicted from measuring of LV volume/mass ratio. In our series of HCM patients, exclusion of patients with significant LVOT gradient did not dramatically change the results.

**Conclusions**

LV volume/mass ratio correlated with flow propagation velocity, early diastolic IVPGs, and UntwR even after adjusting for preload and relaxation. This indicates that these diastolic function parameters have a previously unrecognized source of variability that is independent of both intrinsic diastolic function (characterized by $\tau$) and filling pressures. Because it is easy to calculate and clinically meaningful, LV volume/mass ratio should be considered when assessing patients suspected of LV diastolic dysfunction regardless of LV systolic function.

**Supplementary material**

Supplementary material is available at European Heart Journal Online.

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